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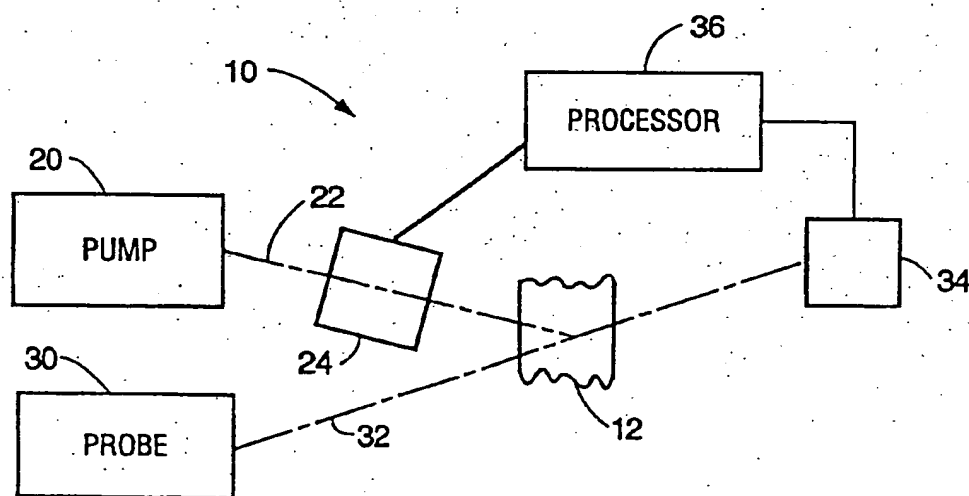
(57) Abstract

An apparatus for the non-invasive analysis of non-homogenous samples is disclosed. The apparatus is particularly suited for analyzing biological samples having different constituents. An intensity modulated light beam is used to preferentially heat a selected constituent in the sample. This periodic heating will create thermal waves in the sample. A probe beam is directed to interact with the sample in the region which has been periodically heated. A phase synchronous detector is used to monitor the periodic changes in the probe beam caused by the thermal waves in the sample. In the preferred embodiment for monitoring blood glucose levels, the wavelength of the modulated light beam is selected to be absorbed in the hemoglobin of the red blood cells. The modulation frequency of the light beam is selected to set the thermal diffusion length of the thermal waves to permit interaction with the glucose molecules in the blood plasma. In addition, the phase synchronous detector is configured to monitor signals which occur ninety degrees out of phase with the modulation of the heating beam. In this manner, the output from the system can be most accurately targeted to the constituent of interest.

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APPARATUS FOR NON-INVASIVE
ANALYSES OF BIOLOGICAL COMPOUNDS

Technical Field

The subject invention relates to a device for
the non-invasive analyses of particular constituents
in a non-homogeneous sample. The apparatus can be
used for the in-vivo monitoring of glucose levels in
the blood stream of a patient.

Background of the Invention

There has been significant interest in
developing devices which permit the non-invasive
monitoring of constituents in the blood and tissues
of the body. Some success has been achieved in
designing devices which measure the oxygen content in
the blood. The devices are known as oxymeters.

Oxymeters determine the level of oxygen in the
blood by measuring the amount of light absorbed in
the tissue. In operation, a probe beam is generated
having a wavelength in the 400 to 600 nanometer
range. The probe beam is directed through the tissue
into the blood stream. The portion of the blood
stream carrying oxygen (oxyhemoglobin) has a high
level of absorption in this wavelength range. Non-
oxygenated hemoglobin and other human tissue are much
more transmissive at these wavelengths. Accordingly,
by measuring the level of absorption which occurs
when the probe beam light passes through the tissue,
the level of oxygen in the blood can be determined.

This approach for the non-invasive analysis of
oxygen content in the blood has been relatively
successful due to a few factors. First, there is a
considerable amount of blood present in the human
body (ten percent) and the red blood cells, which
contain the hemoglobin, account for forty-five
percent of the total volume of the blood. In

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addition, and as noted above, certain light
wavelengths exist which are highly absorbed in
oxygenated blood and which have much lower absorption
levels in the other constituents of the body.

5   Attempts to use optical absorption schemes to
analyze other constituents in the body have been much
less successful because the conditions are less
favorable. For example, many other constituents of
interest are present in much lower concentrations in
10   the body. Moreover, even though the constituents of
interest will have certain specific absorption bands,
these absorption bands are typically shared with
other constituents in the body. Therefore, isolation
and measurement of particular constituents by optical
15   absorption has not been possible.

One constituent in the body for which there is
great interest in developing non-invasive monitoring
techniques is glucose, since monitoring glucose
levels can significantly aid in the treatment of
20   diabetes. It is now well established that a
principal method of preventing some of the more
serious effects of diabetes is to regularly monitor
the glucose level in the blood stream and then
maintain that level within a normal range. At the
25   present time, the most common method for monitoring
glucose levels requires obtaining a small blood
sample. The blood sample is then subjected to a
chemical reaction wherein the glucose is oxidized to
form gluconic acid, hydrogen peroxide and a hydronium
30   ion. This reaction can be monitored using dry
chemical strips either spectrophotometrically or
electrochemically.

The use of the glucose strip method has become
quite common. Unfortunately, this approach is
35   painful, messy, complex, expensive and prone to
error. In addition, since the skin must be pierced

and blood drawn, issues regarding the spread of life
threatening infections arise.

Efforts are underway to provide alternatives to
the blood-glucose strip method. At the present time,
attempts are being made to monitor glucose levels in
saliva, sweat, subcutaneous tissue and the eye.
However, glucose concentrations, particularly in the
saliva and sweat, lag in time behind the actual
concentrations in the blood and therefore do not give
an accurate picture of current glucose levels in the
blood.

To avoid these problems, efforts have been made
to measure blood glucose in a non-invasive manner
using optical techniques similar to those used in
measuring oxygen levels in the blood. One method
relies upon shining near infrared light through a
finger or earlobe. Unfortunately, while the glucose
molecule absorbs in this wavelength region, other,
more highly concentrated constituents in the body
(such as water and proteins) absorb in this
wavelength region as well. Thus, the absorption
caused by glucose is minimal compared to the total
absorption of other constituents.

Even with this minimal absorption, some positive
results can be achieved by applying various forms of
statistical analyses to the measurements. More
specifically, by collecting data and comparing it to
a calibration model, some initial success has been
achieved. However, to date, various factors which
tend to reduce the accuracy of the results have not
been fully resolved. These factors include tissue
temperature, endogenous metabolites, hemoglobin
concentration, repeatability of the placement of the
tested region (finger, earlobe) in the testing device
and subject to subject variability.

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Another technique for the non-invasive
monitoring of glucose is based on the optical
activity of the molecule. Glucose, like many other
carbohydrates and monosaccharides is optically
5   active. When polarized light is passed through a
mixture including an optically active constituent,
the axis of polarization of the light will be rotated
by an amount proportional to the concentration of the
optically active constituent. For typical glucose
10   levels in the blood (approximately 100mg/dL), the
optical rotation of light will be only 5 to 9
millidegrees per centimeter path length.

Prior art polarimeters are capable of measuring
optical rotation at this low level. However, the
15   various elements of the body, including tissue, blood
etc. scatter, absorb and depolarize light, such that
the polarization rotation induced by the glucose will
be masked. To minimize these problems, efforts have
been made to monitor the optical activity of glucose
20   by measuring the effect in the eye where scattering
and absorption is minimized.

These latter efforts have provided some
promising results. However, problems with scattering
and absorption still exist. Moreover, the eye
25   exhibits birefringence which also interferes with the
measurement. Finally, it is unknown how comfortable
patients will be shining lights into their eyes to
measure glucose levels.

Accordingly, there is still a strong need to
30   develop an accurate, non-invasive technique for
monitoring glucose levels in the blood.

The invention described herein addresses this
need through the use of a thermal wave excitation and
detection system. The concept and approaches for
35   evaluating samples using a thermal wave type analysis
are well established today. Commercial thermal wave

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detection systems are employed primarily in the
semiconductor fabrication field where the devices are
used to monitor ion implant dosage, defects and other
features. Examples of such systems can be found in
the following U.S. Patents Nos. 4,521,118; 4,522,510;
4,636,088; 4,579,463; 4,634,290 and 4,632,561.

In general, thermal wave detection systems
include a means for creating a periodic heating in
the sample. In the case of the equipment discussed
above, the preferred heat source is an intensity
modulated laser beam which can be tightly focused to
the micron range important for semiconductor
analysis. The periodic heat source functions to
generate periodic thermal waves which propagate
outwardly interacting with various features in the
sample. These thermal waves will function to
periodically vary a number of different physical and
optical parameters of the sample such as
reflectivity, transmission, absorption, scattering
and local deformation of the sample surface.

The variations of these different parameters can
be monitored using a number of different techniques.
In the systems discussed above, the optical
parameters are investigated using a probe beam of
radiation which is also focused onto the sample.
Periodic changes in the probe beam, such as reflected
power, transmitted power or scattering, are monitored
using a phase synchronous detection system. These
periodic changes can provide valuable information
about the surface and subsurface characteristics of
the sample.

In the past, thermal wave techniques also have
been used experimentally to analyze biological
samples. These experiments have been primarily
limited to photoacoustic spectroscopy experiments
wherein the sample is heated with a modulated optical

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beam and the periodic absorption of this probe beam
as a function of wavelength is measured. For a more
complete discussion, see Photoacoustics and
Photacoustic Spectroscopy, Allan Rosenscwaig, Wiley
Interscience, 1980.

5 The prior investigations of both semiconductors
and biological material relate to samples where it is
relatively straightforward to target the constituent
of interest. For example, when investigating ion
10 dopant levels in semiconductors, the sample is
treated as a uniform absorber of the pump beam and
probe beams. The output signal is a function of a
fairly homogeneous local region of the sample. In
contrast, and as noted above, the blood stream can
15 include a number of different constituents which
inhibits the analysis of specific constituents of
interest.

 Accordingly, it is an object of the subject
invention to provide an improved thermal wave
20 generation and detection system which is particularly
suited for investigating characteristics of non-
homogeneous samples.

 It is a further object of the subject invention
to provide a system which can preferentially analyze
25 selected constituents of a non-homogeneous sample.

 It is another object of the subject invention to
provide a system for analyzing particular
constituents in the blood stream of a mammal.

 It is still a further object of the subject
30 invention to provide a system for the non-invasive
monitoring of the glucose levels in the blood stream
of a mammal.

 It is still another object of the subject
invention to provide a thermal wave detection system
35 which provides spatial discrimination permitting

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analysis of selected constituents in a non-homogeneous sample

Summary of the Invention

In accordance with these and other objects, the subject invention provides for a method and apparatus for analyzing the properties of a non-homogeneous sample, such as blood, which includes two or more constituents. The apparatus includes a means for periodically heating one of the constituents of the sample in a manner to create thermal waves. In one preferred embodiment, the heating means is defined by an intensity modulated light beam which is directed through the tissue in a relatively transparent blood carrying region of the body such as a finger or ear lobe.

The effects of the thermal waves generated in the sample on the constituent of interest are then monitored. These effects can be monitored optically in a known manner. For example, a probe beam can be used to measure periodic changes in transmission, absorption, reflection or scattering. Other detection schemes which rely on acoustics (ultrasound), microwaves or even magnetic resonance imaging (MRI), could be used. The monitoring approach will include a phase synchronous detector for measuring changes which occur at a frequency related to the periodicity of the heating means. As described in the references cited above, monitoring the periodic response in a phase synchronous fashion can greatly improve sensitivity.

In order to target the measurement to the constituent of interest and provide the necessary spatial discrimination, a few distinct parameters of the system should be carefully selected. First, the periodic heating source can be selected to

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preferentially heat one of the constituents in the
sample. When the heating source is an intensity
modulated light beam, the wavelength of light
selected should be preferentially absorbed in the
selected constituent. Similarly, if the detection
system relies upon the measurement of the modulated
transmission of a probe light beam, the wavelength of
the probe should be preferentially absorbed in the
constituent to be analyzed.

    In accordance with the subject invention, the
modulation frequency of the heating source should
also be carefully controlled to maximize the signal
from the target constituent. More specifically,
thermal waves will be created in the constituent
which absorbs the heating from the heat source.
These thermal waves will then propagate outwardly in
a spherical wavefront from the heated constituents.
Thermal waves are inherently critically damped and do
not travel very far. However, the length of travel
(or thermal diffusion length μ) is a direct function
of the modulation frequency of the heating source.
If the target constituent and the heated constituent
are the same, then the heating frequency should be
selected to minimize the thermal diffusion length so
that any heating effects will be confined to the
heated constituent. If the target constituent is
different from the heated constituent, then the
heating frequency should be selected so that the
thermal waves propagate a sufficient distance to
reach and interact with the target.

    In still another aspect of the subject
invention, the phase discrimination of the detection
system should also be controlled to maximize the
signal strength from the target constituent. More
specifically, the approach used in most prior art
thermal wave analyses was to measure signals which

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are in phase with the thermal wave signals. These
are the signals which are at their strongest at the
center of the locations which are being periodically
heated. A thermal wave signal also exists which is
ninety degrees out of phase ($\phi = \pi/2$) from the "in-
phase" (or ϕ = zero) signal. The $\pi/2$ signal is
typically weaker than the in-phase signal. However,
in the case where the target constituent is not the
same as the constituent which has been heated, the
frequency of the heating source can be selected so
that the locus of the $\pi/2$ signal will coincide with
the location of the target constituent rather than
the heated constituent. By measuring the $\pi/2$ signal,
information about the target constituent can be more
readily evaluated.

It should be noted that the prior art does
disclose the concept of varying the frequency of the
modulated heat source in order to vary the diffusion
length of the thermal waves. (See, for example, U.S.
Patent No. 4,513,384). In addition, there has also
been some general discussion of the concept of
adjusting the phase relationship between the lock-in
detector and the pump modulator in thermal wave
systems. (See, for example, "Depth Profiling of
Integrated Circuits with Thermal Wave Electron
Microscopy," Rosencwaig, Electronics Letters, Vol 16,
No. 24, November 20, 1980, page 928-930.) However,
these disclosures were in the context of providing
depth profiling of the sample, rather than attempting
to isolate and enhance the measurement of specific
constituents in a non-homogeneous sample. In
addition, these depth profiling studies did not
disclose the concepts of preferentially heating
selected first constituents in the sample; selecting
the modulation frequency of the heating source so
that the thermal waves will interact with selected

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second constituents spaced away from the first
constituents and then monitoring the $\pi/2$ phase signal
to maximize detection of information related to the
second constituents.

5   Further objects and advantages of the subject
invention will become apparent from the following
detailed discussion taken in conjunction with the
drawings in which:

Brief Description of the Drawings

10   Figure 1 is a schematic diagram of a thermal
wave detection system formed in accordance with the
subject invention.

        Figures 2a, 2b and 2c illustrate how variations
in the thermal diffusion length can be used to target

15   selected constituents in a sample.

        Figure 3 is schematic representation of a tissue
cell.

        Figure 4 is a schematic representation of a red
blood cell.

20   Figure 5 is a schematic representation of red
blood cells in a blood vessel.

        Figure 6 is a schematic diagram of a thermal
wave detection system for measuring the optical
activity of a molecule.

25   Figure 7 is a cross-sectional illustration of a
tissue sample, including a blood vessel.

        Figure 8 is a schematic diagram of a thermal
wave detection system for monitoring the modulated
optical reflectance of a probe beam.

30   Figure 9 is a schematic diagram of a thermal
wave detection system for monitoring the modulated
optical scattering of a probe beam.

        Figure 10 is a schematic diagram of a thermal
wave detection system utilizing a double modulated

35   pump and probe beam combination.

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Figure 11 is a schematic diagram of a thermal
wave detection system wherein the thermal wave
effects are monitored with non-optical detection
devices.

5   ## Detailed Description of the Preferred Embodiments

Figure 1 illustrates a basic lay-out of a system
10 for generating and detecting thermal waves in a
sample 12. The system 10 includes a means for
periodically heating the sample. In this embodiment,
10   the means includes a pump source 20 generating a beam
of light 22. The beam of light 22 is passed through
a modulator 24 for intensity modulating the beam at a
predetermined frequency ω. The pump beam 22 is
directed into the sample in a manner so that certain
15   constituents therein are periodically heated.

The subject device further includes a means for
monitoring the periodic effects of the thermal waves
on the sample and generating an output signal in
response thereto. In this embodiment, the monitoring
20   means includes a probe source 30 for generating a
beam of light 32. The probe beam 32 is directed
through the sample and strikes a photodetector 34.
The output of the photodetector is fed to a processor
36 which also receives an input from the modulator
25   24. The processor 36 functions to extract the
portion of the photodetector signal which is phase
synchronous with the periodic heating in the sample.
In this sense, the detector and processor function
together to isolate a phase synchronous signal and
30   generate an output representative of the thermal wave
interaction with the sample. The processor can also
be programmed to analyze this phase synchronous
output to determine properties of the sample.
Thermal wave detection systems operating in a manner
35   similar to that described above (except with

reflected rather than transmitted light) have been
successfully developed and sold for measuring dopant
concentrations in semiconductor wafers.

 5   The basic thermal wave detection scheme can be
enhanced in order to analyze samples having multiple
constituents with overlapping responses. In
accordance with the subject invention, an approach is
used which permits spatial discrimination of various
constituents in the sample.

10   The subject approach is designed to address a
typical non-homogeneous sample of the type associated
with biological compounds. A one-dimensional model
of such a system is shown in Figure 2. This model
can be useful in considering both a solid system such

15   as human tissue as well as the constituents in a
flowing liquid such as the blood stream. In either
case, the spacings illustrated can be considered
average spacings between constituents which are
statistically representative of the actual

20   distribution in the sample.

          In this single axis representation, elements X,
Y and Z are dispersed throughout the sample. If a
non-discriminatory heat source were to be used,
thermal waves would be generated uniformly across the

25   sample and no spatial discrimination would be
possible.

          In accordance with the subject invention, a
periodic heat source is chosen which can selectively
heat a particular constituent. In this example, a

30   heat source is selected which is preferentially
absorbed in constituent X. The periodic heating of
constituent X will cause spherical thermal waves 40
to be generated emanating from each of the
constituent X sites.

35   In Figure 2a, the thermal waves 40 are shown
with a relatively short diffusion length. This short

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diffusion length corresponds to a higher modulation
frequency of the heating source. As can be seen, the
thermal waves are concentrated in the region of
constituent X and interact only slightly with the
adjacent constituents Y. Accordingly, if a standard,
phase-locked thermal wave signal is measured, it will
necessarily correspond primarily to the interaction
of the thermal waves with constituent X.

    The subject system can also be configured to
investigate a target constituent which is different
and spatially separated from the constituent that has
been periodically heated. This approach is shown in
Figures 2b and 2c.

    In Figure 2b, the diffusion length of the
thermal wave 42 has been increased. This can be
accomplished by lowering the modulation frequency of
the heating source. In this case, the thermal wave
will interact strongly with both constituents X and
Y, and only slightly with constituent Z. In Figure
2c, the diffusion length of the thermal wave 44 has
been increased still further, also by lowering the
modulation frequency of the heating source. In this
situation, the thermal waves 44 will interact with
all three constituents, X, Y and Z.

    In order to extract information about a
constituent which is spatially separated from the
constituent which is being heated, the thermal wave
signal which is ninety degrees out of phase with the
periodic heating is measured. This fact can best be
appreciated by recognizing that (for a one-
dimensional model) the strength of the thermal wave
signal is given by the following equation:

(1) $T_{(x)} = T_0 e^{-x/\mu} \cos[\omega t - (x/\mu)]$

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where x is the distance from the periodic heat
source, μ is the thermal diffusion length, ω is the
radial modulation frequency and t is time.   The bulk
of the signals which can be detected that are exactly
5   in-phase with the periodic heat source ($\phi = \omega t =$
zero) will result primarily from the thermal wave
interaction with the sample in the region coinciding
with the origin of the periodic heating. On the
other hand, the bulk of the signals which can be
10   detected that are ninety degrees out of phase with
the periodic heat source ($\phi = \omega t = \pi/2$) will result
primarily from the thermal wave interaction with the
sample roughly one thermal diffusion length away from
the origin of the periodic heating.
15   Thus, if there was interest investigating
constituent Y, the thermal diffusion length could be
set as shown in Figure 2b and the thermal wave signal
should be measured at $\pi/2$ with respect to the
periodic heating. By this arrangement, the thermal
20   wave signal will be predominated by the interaction
between the thermal waves and constituent Y.
Similarly, if there was interest in investigating
constituent Z, the thermal diffusion length could be
set as shown in Figure 2c and the $\pi/2$ signal
25   measured. It should be understood that in the
context of the specification and claims, monitoring a
signal which is close to, but not exactly ninety
degrees out of phase with the periodic heat source,
would produce similar results.
30   The signal separation for different constituents
can be maximized by setting the thermal diffusion
length to maximize the $\pi/2$ signal with respect to the
in-phase signal. This ratio is maximized when the
thermal diffusion length is set to be equal to
35      $(2/\pi)d$, where d is the spacing between the

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constituents X and Y. This relationship can be shown
by the following

$$(2) \quad T(d, \phi = 0) = T_0 e^{-d/\mu} \cos(d/\mu)$$

$$(3) \quad T(d, \phi = \pi/2) = T_0 e^{-d/\mu} \sin(d/\mu)$$

$$(4) \quad \frac{T(d, \phi = \pi/2)}{T(d, \phi = 0)} = \tan(d/\mu)$$

The ratio of equation (4) is maximized when
$(d/\mu) = \pi/2$.

The general formula for determining the thermal
diffusion length μ in a material is as follows:

$$(5) \quad \mu = (2\kappa/\rho C\omega)^{\frac{1}{2}}$$

where:

κ = thermal conductivity (calories/cm-sec-°C)
ρ = density (grams/cm^3)
C = specific heat (calories/gram-°C)
ω = radial modulation frequency ($2\pi f$)

Since most biological matter is composed mainly
of water, a fairly accurate approximation of the
thermal diffusion length in biological matter can be
derived using the thermal properties of water as
follows:

κ = 1.4 x 10^{-3} calories/cm-sec-°C
ρ = 1.0 grams/cm^3
C = 1.0 calories/gram-°C

Using equation (5) above, the thermal diffusion
length μ in biological tissue will be as follows for
the modulation frequencies set forth below:

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100 Hz $\mu \sim$ 21 microns
1 kHz $\mu \sim$ 6.6 microns
10 kHz $\mu \sim$ 2.1 microns
100 kHz $\mu \sim$ 0.66 microns
1 mHz $\mu \sim$ 0.2 microns

To further enhance the ability to discriminate between selected constituents, it may also be desirable to carefully select the wavelength of the probe light source. More specifically, in cases where the modulated transmission of the probe beam light is being monitored, the wavelength of the probe light source should, if possible, be selected to be preferentially absorbed in the constituent of interest. As noted above, the absorption spectra for many biological materials overlap, such that proper selection of the probe beam wavelength cannot alone provide adequate discrimination. However, as an added parameter to the selection criteria discussed above (including selection of the pump beam wavelength, modulation frequency and phase discrimination), proper selection of the probe beam wavelength can further enhance the detection system.

In order to obtain even more accurate results, it would be desirable to use more than one wavelength for the probe beam. More specifically, thermal wave data generated at a plurality of wavelengths can help reduce measurement ambiguities. Although low cost portable test devices may be limited to the use of a single probe beam wavelength, to the extent the subject invention is used for office or laboratory testing, spectroscopic capabilities would be desirable.

There are a wide variety of body structures and systems which could be analyzed using a thermal wave detection device which permits spatial

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discrimination. For example, the subject system could be used to monitor constituents within individual body cells. Figure 3 is graphic representation of a typical cell 50 having a nucleus 52 and many other constituents (54, 56 and 58) within the cell membrane 60. By properly selecting the wavelengths of the pump and probe beams, the modulation frequency of the pump beam and phase discrimination of the processor, selected regions within the cell can be preferentially examined.

For example, if it were desired to investigate the protein constituents residing in the nucleus without interference from the protein constituents found in the cell fluid or cell membrane, the wavelength of the pump source would be selected to preferentially excite at least one constituent in the nucleus. The pump modulation frequency would be set relatively high (eg. one mHz) so that the thermal diffusion length would be about 0.2 microns, short enough so that the thermal waves would not propagate much beyond the nucleus. Measurements would then be taken in phase with the excitation source (ϕ = zero). Conversely, if it were desired to investigate the proteins outside of the nucleus, a lower modulation frequency could be used and detection would be carried out with the $\pi/2$ signal.

The general concepts described above can be used to obtain information about specific constituents of interest. For example, the subject system could be used to monitor the oxygen level in the blood. A typical blood cell 66 is shown in Figure 4. Unlike other cells in the body, mature blood cells do not include nuclei. Hemoglobin molecules 68 are the principle constituent in blood cells. These hemoglobin molecules are the primary carriers of oxygen for the blood and are uniformly distributed in

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the interior of the red blood cells. Oxygenated
hemoglobin molecules absorb light in the 400 to 600
nanometer range. Accordingly, these molecules can be
preferentially heated using a pump beam of that
5   wavelength.

        Assuming that the hemoglobin in the red blood
cells is the constituent of interest, the pump beam
will be modulated at a relatively high frequency so
that the thermal waves will not propagate much beyond
10   the walls of the red blood cells. As discussed in
more detail below, red blood cells have a size in the
micron range, so a modulation frequency of about 100
kHz could be selected. As noted above, a modulation
frequency of 100 kHz will produce thermal waves
15   having a diffusion length of about 0.66 microns which
should effectively confine the signal to the red
blood cells. The detector will be phase synchronized
with the modulation frequency of the pump beam at ϕ =
zero.

20   If the constituents of interest are not the
hemoglobin molecules of the red blood cells, but
constituents outside the red blood cells, then the
thermal diffusion length should be increased by
lowering the modulation frequency of the pump beam.
25   A specific example of this alternative approach is
discussed below with respect to glucose monitoring.

        To distinguish between the pump and probe beams,
it would be desirable to use two different
wavelengths. In this manner, an optical filter can
30   be placed in front of the detector to block light
from the pump beam. For this application, although
the wavelengths of the pump and probe beams should be
different, it would be desirable if both beams fell
within absorption range for hemoglobin.

35   Other approaches could be used to distinguish
between the pump and probe beams. For example, the

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beams could be polarized along different axes
allowing the pump beam to be filtered from the
detector with a suitable linear polarizer. It would
also be possible to shorten the diffusion length of
5   the thermal-wave and measure the $\pi/2$ signal which
corresponds to a location where the contribution from
the pump will be close to zero and any detected
signal will be a result of the thermal wave response
in the probe. Another alternative, discussed in more
10   detail below, is to modulate both the pump and probe
beams at two different frequency and detect a
periodic response in the combined output beams at a
sum or difference frequency.

In a further aspect of the subject invention,
15   measurement accuracy can be enhanced by taking
measurements both in phase and ninety degrees out of
phase. The pump modulation frequency would be
selected so that the thermal diffusion length was
equal to about one-half the distance between the red
20   blood cells. In this case, the ϕ = zero signal will
be a function of the red blood cells along with other
tissue variables while the $\pi/2$ signal will primarily
be a function of the other tissue variables excluding
the red blood cells. The $\pi/2$ signal can now be used
25   to normalize the ϕ = zero signal to obtain more
accurate results.

The concept of setting the thermal diffusion
length to be equal to one-half the distance between
red blood cells is also useful for evaluating
30   constituents in the blood plasma. More specifically,
and as noted above, most plasma constituents of
interest (such as glucose) cannot be preferentially
excited with a specific wavelength. In fact, the
primary absorption bands of glucose are similar to
35   the even stronger absorption bands of the more

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prevalent water molecule which will prevent selective
excitation.

Therefore, in accordance with the subject
invention, a system can be set up where the thermal
waves are generated in the hemoglobin of the red
blood cells using a pump beam having a wavelength in
the 400 to 600 nanometer range. The modulation
frequency of the pump is set so that thermal
diffusion length is on the order of one-half the
distance between red blood cells. In addition, the
detection scheme is set up to measure the $\pi/2$ signal
which will primarily correspond to the locations
outside the red blood cells. In this manner, a
signal from the constituents in the blood plasma can
be generated.

In order to determine the proper modulation
frequency, a simplified framework for the
distribution of red blood cells 66 in a blood vessel
72 can be constructed in a manner shown in Figure 5.
Most red blood cells are roughly in the form of
disks. In the illustrated model, the disks are lined
up end to end. The average thickness of these disks
is known to be about 1.9 microns. In this model, the
interlayer spacing is defined as d_1. Since blood
cells account for about forty-five percent of the
blood volume, the volume of red blood cells per cubic
centimeter is 0.45 cm^3. Therefore, on average, the
spacing between the red blood cells should be

$$(5) \quad d_1 = 1.9/0.45 = 4.22 \text{ microns}$$

Based on this calculation, the thermal diffusion
length should be one-half of 4.22 microns or 2.11
microns. Assuming the blood consists primarily of
water molecules, the modulation frequency should be
on the order of 10 kHz and measurements should be

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taken at $\pi/2$ to target the constituents in the
plasma.

All of the examples above have thus far been
limited to measuring the periodic absorption of the
probe beam in the sample. This approach could be
used for glucose as well. However, for glucose, it
also would be possible to combine the proposed
thermal wave excitation technique with the technique
for measuring optical activity of the glucose
molecule.

As noted above, glucose is optically active and,
therefore, the glucose in the plasma will function to
rotate the polarization of an incoming probe beam.
The amount of polarization rotation produced by a
normal blood glucose concentration of 100 mg/dl is
quite small (5 to 9 millidegrees per centimeter path
length). Fortunately, glucose is the only
constituent in the human body which will cause any
measurable rotation. Unfortunately, prior art
polarimeter techniques for measuring the optical
activity of glucose have met with limited success.
The principal problems with the prior art approaches
related to low signal strength and depolarization
effects of the skin.

It is believed that the thermal wave modulated
response will enhance the available signal making
detection easier for a number of reasons. First,
using the schemes set forth above, including the
proper selection of the thermal diffusion length and
analyzing the $\pi/2$ signal, the response can be more
accurately targeted to the glucose molecule in the
plasma. Secondly, it is believed that the modulated
signal will be much less affected by the
depolarization effects which interfere with and
weaken a typical DC signal.

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The preferred embodiment for monitoring glucose
levels based on the modulated optical activity level
of the sample is illustrated in Figure 6. In this
device 100, the blood 112 can be excited with a

5   periodic heat source 120. As presently conceived,
the optimum source would consist of a light beam 122
having a wavelength selected to excite oxyhemoglobin
in the red blood cells. The thermal diffusion length
would be set to about 2.1 microns, or one-half the

10   spacing between red blood cells. As noted above,
this result can be achieved with a modulation
frequency of about 10 kHz generated by a modulator
124.

A probe light source 130 is provided generating

15   a probe beam 132 having a wavelength selected to
maximize transmission through the tissue. Note that
in this case, where modulated optical activity,
rather than modulated absorption is being measured,
the selection of the probe beam wavelength should

20   minimize absorption in the tissue in order to
maximize signal strength. Suitable probe beam
wavelengths would fall in the visible regions of the
spectrum.

The probe beam 132 is first passed through a

25   linear polarizer 133 and then into the tissue. A
detector 134 is provided which would function to
measure the change in polarization state of the beam
induced by the passage through the body. A variety
of devices exist for measuring the changes in the

30   polarization state of beam. Such devices, generally
referred to a polarimeters, are described in greater
detail in <u>Ellipsometry and Polarized Light</u>, Azzam and
Bashara, North Holland, 1977. These devices usually
include a "polarization analyzer" and a

35   photodetector. The output of this detector is fed to
a processor 136 along with the output of the

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modulator 124. The modulated optical activity of the sample can then be derived. Since the glucose is located in the plasma, the $\pi/2$ signal should be used.

In addition to rotating the plane of
5   polarization of linearly polarized light, the optical activity of glucose in solution will also modify the characteristics of circularly polarized light. More specifically, the transmission characteristics of glucose in solution will be different for right and
10   left-hand circularly polarized light. This property is referred to as circular dichroism. In the prior art, this property has been evaluated by alternately transmitting right and left-hand circularly polarized light through an optically active medium and
15   measuring the transmission ratio between the polarizations. This transmission ratio can be used to determine the concentration of the glucose in the blood.

In accordance with the subject invention,
20   glucose levels can be monitored by measuring the modulated circular dichroism in the sample. The apparatus would be similar to that shown in Figure 6. In this case, the wavelength of the probe beam would be selected to match an absorption band in the
25   glucose (for example, in the near-infrared region). In addition, a rotatable quarter-wave plate 135 (shown in phantom line) would be positioned in the path of the probe beam following the linear polarizer 133. The rotational position of the quarter-wave
30   plate would be alternately changed to alternately generate right and left-hand circularly polarized light. The amount of light transmitted through the tissue would be measured by detector 134. The output of this detector is fed to the processor 136 which
35   can calculate the ratio of the transmitted left and right-circularly polarized light.

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In the prior art, circular dichroism would be
monitored as an AC signal based on the rotation of
the quarter-wave plate 135.   In this case, the
processor is connected to the modulator 124 allowing

5   phase synchronous detection of modulated variations
in the circular dichroism which occur in response to
the periodic heating.   Assuming the hemoglobin is
being heated, the $\pi/2$ signal would be used.

The subject invention can also be utilized to

10   investigate constituents in the tissue surrounding a
blood vessel.   Figure 7 illustrates a region in the
tissue having a blood vessel 72 carrying blood cells
66.   A layer of a first type of tissue 74 is shown
surrounding the vessel.   A second layer of tissue 76

15   surrounds the first layer.

In accordance with the subject invention,
constituents in the first layer 74 can be
investigated by proper selection of the pump and
probe beams as well as the phase discrimination of

20   the detector.   For this application, the pump beam
can be selected to excite the hemoglobin molecules in
the red blood cells in the vessel 72.   The modulation
frequency of the pump beam is chosen to create a
thermal diffusion length that would permit the

25   thermal waves to interact with layer 74.   A probe
beam wavelength will be selected which maximizes the
absorption in layer 74.   The processor will be
arranged to monitor the $\pi/2$ signal.   In this manner,
information about the constituents in layer 74 can be

30   derived.

In each of the embodiments discussed above, the
detector was arranged to measure the probe beam after
it has been transmitted through the sample.   In the
past, the thermal wave response has also been

35   monitored using both reflection and scattering
detection techniques.

25

Figure 8 is a schematic diagram of a thermal
wave system for monitoring the modulated optical
reflectance of a probe beam. In this example, a pump
source 220 generates a pump beam 222 which is passed

5   through a modulator 224 to periodically heat selected
constituents in the sample 12. A probe source 230
generates a probe beam 232 which is reflected off the
sample. A detector 234 is provided to monitor the
power of the specularly reflected beam. To the

10   extent that the thermal waves modulate the optical
reflectivity of the sample, a modulated output will
be generated by the detector. As in the previous
embodiments, the output of the detector is supplied
to the processor, along with the output from

15   modulator to allow phase synchronous detection.
Figure 9 is a schematic diagram of a thermal
wave detection system that relies on the measurement
of the scattering of the probe beam. A pump source
320 generates a pump beam 322 which is passed through

20   a modulator 324 to periodically heat selected
constituents in the sample 12. A probe source 330
generates a probe beam 322 which is directed to the
sample as well. Detector 334 is positioned in a
manner to measure non-specularly reflected light from

25   the probe beam which has been scattered after
interaction with the sample.
To the extent the sample is periodically heated,
periodic changes in the complex index of refraction
and possibly deformations at the sample surface will

30   occur in response to the thermal waves in the sample.
These effects will modulate the optical scattering of
the probe beam. This principal is discussed in
greater detail in U.S. Patent No. 4,632,561. The
output of the detector 334 is supplied to a processor

35   336. In the manner described above, the sample can

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be analyzed through a phase synchronous detection
scheme.

Figure 10 shows an alternate approach wherein
the functions of the pump and probe beams are
5   combined. In this system, two pump sources 420 and
421 are provided for generating beams 422 and 423.
Each of the pump beams is passed through a separate
modulator 424 and 425 for imposing two distinct
modulation frequencies ω_1 and ω_2. These two beams are
10   then combined with appropriate optics and passed
through the sample 12 to periodically heat selected
constituents therein. The modulated transmitted (or
reflected) power of the combined beams is measured by
detector 434. The modulated transmittance (or
15   reflectance) signals will be present at both the two
pump frequencies ω_1 and ω_2, as well as the cross
products $(\omega_1 + \omega_2)$ and $(\omega_1 - \omega_2)$. Preferably, the
phase synchronous detection is carried out at the
difference frequency which will be lower than and
20   different from either of the two pump frequencies.
Further details relating to this type of dual
frequency pumping process can be found in U.S. Patent
Nos. 5,206,710 and 5,408,327.

All of the embodiments discussed so far have
25   included a means for optically monitoring the thermal
wave response in the sample. Other approaches for
monitoring the thermal wave response can also be
used. Figure 11 illustrates a generic schematic
diagram for such a system. As in the previously
30   described systems, a pump source 530 is provided for
generating a pump beam 532. The pump beam is passed
through a modulator 534 and then directed to the
sample to periodically heat selected constituents
therein. The periodic heating will affect a number
35   of parameters in the sample which could be measured
by various detectors 534. For example, detector 534

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could consist of an ultrasonic imager for
transmitting acoustic waves into the sample. In an
ultrasonic imager, the reflected or scattered
acoustic waves are measured to provide information
5   about the sample. In accordance with the subject
invention, the ultrasound response that occurs at the
periodic excitation frequency can be extracted to
isolate the thermal wave effects. It would also be
possible to use detector systems based on microwaves
10   or magnetic resonance imaging. In all cases, the
modulated response should be determined. In
addition, in order to analyze constituents of
interest which are separate from the constituents
that have been periodically heated, it would be
15   desirable to select an appropriate modulation
frequency and to isolate the $\pi/2$ phase signal.

In the illustrated embodiments, an intensity
modulated optical light beam has been used to induce
periodic heating in the sample. Other possible
20   mechanisms for providing the preferential periodic
heating to selected constituents in the sample would
include microwaves, focused ultrasound or X-rays.

While the subject invention has been described
with reference to the preferred embodiments, various
25   changes and modifications could be made therein, by
one skilled in the art, without varying from the
scope and spirit of the subject invention as defined
by the appended claims.

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I CLAIM:

1. An apparatus for analyzing the properties of
a sample, said sample being non-homogeneous and
including at least first and second constituents,
said apparatus comprising:
        means for selectively including a periodic
    heating in said first constituents in the sample
    in a manner to create thermal waves therefrom;
        a phase synchronous detector for monitoring
    the periodic effects of the thermal waves on the
    sample and generating an output signal; and
        processor means for analyzing the sample
    based on the output signal generated by said
    detector and with the frequency of the periodic
    heating and the phase discrimination of the
    detector being selected to target the analysis
    to one of the first or second constituents in
    the sample.

2. An apparatus as recited in claim 1 wherein
the frequency of the periodic heating is selected so
that the spread of the thermal waves is primarily
confined to the first constituents.

3. An apparatus as recited in claim 1 wherein
the detector is configured to monitor the periodic
effects of the thermal waves which are in-phase with
the periodic heating.

4. An apparatus as recited in claim 3 wherein
the detector is configured to also monitor the
periodic effects of the thermal waves which are
approximately ninety degrees out of phase with the
periodic heating and wherein the out-of-phase signals
are used to normalize the in-phase signals.

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5.   An apparatus as recited in claim 1 wherein
the frequency of the periodic heating means is
selected so that the thermal waves will spread and
interact with the second constituents.

5   6.   An apparatus as recited in claim 5 wherein
the detector is configured to monitor the periodic
effects of the thermal waves which are approximately
ninety degrees out of phase with the periodic heating
permitting targeting of the second constituent.

10   7.   An apparatus as recited in claim 6 wherein
the frequency of the periodic heating means is
selected so that the thermal diffusion length of the
thermal waves will be equal to approximately half the
average distance between the first constituents.

15   8.   An apparatus as recited in claim 6 wherein
the frequency of the periodic heating means is
selected so that the thermal diffusion length of the
thermal waves will be equal to approximately $(2/\pi)$
times the average distance between the first and
20   second constituents.

9.   An apparatus as recited in claim 1 wherein
said periodic heating means includes:
          a light source for generating a pump beam
          having a wavelength which is preferentially
25   absorbed in said first constituents of said
          sample;
          means for intensity modulating said pump
          beam at a predetermined frequency; and
          means for directing the pump beam to the
30   sample so that the energy of the pump beam is
          absorbed in said first constituents in a manner
          to generate thermal waves emanating therefrom.

30

10. An apparatus as recited in claim 1 wherein said detector includes an ultrasonic imager.

11. An apparatus as recited in claim 1 wherein said detector includes a microwave generator and detector.

12. An apparatus as recited in claim 1 wherein said detector includes a magnetic resonance imager.

13. An apparatus as recited in claim 1 wherein said detector includes a probe source for generating a probe beam and a means for directing the probe beam to interact with the sample.

14. An apparatus as recited in claim 13 wherein the wavelength of the probe beam is selected to be preferentially absorbed in the targeted constituent.

15. An apparatus as recited in claim 13 wherein the detector functions to measure the modulated power of the probe beam after it has interacted with the sample.

16. An apparatus as recited in claim 13 wherein the detector functions to measure the modulated reflected power of the probe beam.

17. An apparatus as recited in claim 13 wherein the detector functions to measure the modulated transmitted power of the probe beam.

18. An apparatus as recited in claim 13 wherein the detector functions to measure the modulated scattering of the probe beam.

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19. An apparatus as recited in claim 13 wherein the detector functions to measure the modulated changes in polarization state of the probe beam.

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20.   An apparatus for the non-invasive, in vivo
analysis of constituents carried in the blood of a
living mammal, said blood including red blood cells
having hemoglobin therein, said apparatus comprising:

5   a first light source for generating a pump
beam having a wavelength which is preferentially
absorbed in the hemoglobin of red blood cells;
               means for intensity modulating said pump
beam at a predetermined frequency;
10   means for directing the pump beam through
the skin of the mammal and into the blood so
that the energy of the pump beam is absorbed in
the red blood cells in a manner to generate
thermal waves emanating therefrom;
15   a second light source for generating a
probe beam;
               means for directing the probe beam through
the skin of the animal and into the blood;
               a phase synchronous detector for monitoring
20   the periodic changes in the probe beam caused by
the thermal waves in the blood and generating an
output signal; and
               processor means for analyzing the
constituents in the blood based on the output
25   signal generated by said detector and with the
modulation frequency of the pump beam and the
phase discrimination of the detector being
selected to target the analysis to selected
constituents in the sample.

30   21.   An apparatus as recited in claim 20 wherein
the frequency of the periodic heating is selected so
that the spread of the thermal waves is primarily
confined to the red blood cells.

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22.   An apparatus as recited in claim 20 wherein
the detector is configured to monitor the periodic
effects of the thermal waves which are in-phase with
the periodic heating.

5   23.   An apparatus as recited in claim 22 wherein
the detector is configured to also monitor the
periodic effects of the thermal waves which are
approximately ninety degrees out of phase with the
periodic heating and wherein the out-of-phase signals
10   are used to normalize the in-phase signals.

24.   An apparatus as recited in claim 20 wherein
the frequency of the periodic heating means is
selected so that the thermal waves will spread beyond
the hemoglobin to other constituents in the blood.

15   25.   An apparatus as recited in claim 24 wherein
the detector is configured to monitor the periodic
effects of the thermal waves which are approximately
ninety degrees out of phase with the periodic heating
permitting targeting of the other constituents in the
20   blood.

26.   An apparatus as recited in claim 25 wherein
the frequency of the periodic heating means is
selected so that the thermal diffusion length of the
thermal waves will be equal to approximately half the
25   average distance between the red blood cells.

27.   An apparatus as recited in claim 20 wherein
the wavelength of the probe beam is selected to be
preferentially absorbed in the targeted constituent.

28.   An apparatus as recited in claim 20 wherein
30   the detector functions to measure the modulated power

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of the probe beam after it has interacted with the
sample.

29. An apparatus as recited in claim 28 wherein
the detector functions to measure the modulated
reflected power of the probe beam.

30. An apparatus as recited in claim 28 wherein
the detector functions to measure the modulated
transmitted power of the probe beam.

31. An apparatus as recited in claim 20 wherein
the detector functions to measure the modulated
scattering of the probe beam.

32. An apparatus as recited in claim 20 wherein
the detector functions to measure the modulated
changes in the polarization state of the probe beam.

33. An apparatus as recited in claim 20 wherein
the targeted constituent is glucose and wherein said
probe beam is linearly polarized prior to interacting
with the glucose and wherein said detector monitors
the modulated polarization rotation of the beam.

34. An apparatus as recited in claim 33 wherein
the wavelength of the probe beam is selected to be in
the visible region.

35. An apparatus as recited in claim 20 wherein
the targeted constituent is glucose and wherein said
probe beam is alternately left and right-hand
circularly polarized prior to interacting with the
blood stream and wherein said detector monitors the
modulated ratio of the transmitted left and right-
hand circular polarized light of the probe beam.

36. An apparatus as recited in claim 35 wherein
the wavelength of the probe beam is selected to be in
the near infrared range.

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37. An apparatus for the non-invasive, in vivo
analysis of glucose carried in the blood stream of a
living mammal, said blood stream also carrying red
blood cells having hemoglobin therein, said apparatus
5   comprising:

            a first light source for generating a pump
     beam having a wavelength which is preferentially
     absorbed in the hemoglobin of red blood cells;

            means for intensity modulating said pump
10   beam at a predetermined frequency;

            means for directing the pump beam through
     the skin of the mammal and into the blood stream
     so that the energy of the pump beam is absorbed
     in the red blood cells in a manner to generate
15   thermal waves emanating therefrom, with the
     modulation frequency of the pump beam being
     selected so that the thermal waves extend beyond
     the hemoglobin and interact with the glucose in
     the blood stream;

20   a second light source for generating a
     probe beam;

            means for directing the probe beam through
     the skin of the mammal and into the blood
     stream;

25   a phase synchronous detector for monitoring
     the periodic changes in the probe beam caused by
     the thermal waves interacting with the glucose
     in the blood stream and generating an output
     signal responsive thereto, said detector for
30   monitoring the periodic changes in the probe
     beam that are approximately ninety degrees out
     of phase with the periodicity of the thermal
     waves; and

            processor means for analyzing the
35   concentration of glucose in the blood stream

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based on the output signal generated by said
detector.

38. An apparatus as recited in claim 37 wherein
the modulation of the pump beam is selected so that
5   the thermal diffusion length of the thermal waves
will be equal to approximately half the average
distance between red blood cells.

39. An apparatus as recited in claim 37 wherein
said probe beam is linearly polarized prior to
10   interacting with the glucose and wherein said
detector monitors the modulated polarization rotation
of the beam.

40. An apparatus as recited in claim 39 wherein
the wavelength of the probe beam is selected to be in
15   the visible range.

41. An apparatus as recited in claim 39 wherein
said probe beam is alternately left and right-hand
circularly polarized prior to interacting with the
blood stream and wherein said detector monitors the
20   modulated ratio of the transmitted left and right-
hand circular polarized light of the probe beam.

42. An apparatus as recited in claim 41 wherein
the wavelength of the probe beam is selected to be in
the near infrared range.

25   43. An apparatus as recited in claim 37 wherein
the wavelength of the pump beam is between 400 and
600nm.

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44. An apparatus as recited in claim 37 wherein
the modulation frequency of the pump beam is on the
order of 10 kHz.

45. An apparatus as recited in claim 37 wherein
5   the detector functions to measure the modulated
transmitted power of the probe beam.

46. An apparatus as recited in claim 45 wherein
the wavelength of the probe beam is selected to be in
the visible range.

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47.   A method for analyzing the properties of a
sample, said sample being non-homogenous and
including at least first and second constituents,
said method comprising the steps of:

5   generating an intensity modulated pump beam
having a wavelength which is preferentially
absorbed in the first constituents;

               directing the pump beam to interact with
the sample to selectively induce a periodic
10   heating in the first constituents in a manner to
generate thermal waves emanating therefrom, and
wherein the modulation frequency of the pump
beam is selected so that the thermal waves
extend beyond the first constituents and
15   interact with the second constituents;

               generating a probe beam;

               directing the probe beam to interact with
the sample;

               monitoring the periodic changes in the
20   probe beam caused by the thermal waves
interacting with the second constituents and
generating an output signal responsive thereto,
and with the monitored periodic changes being
approximately ninety degrees out of phase with
25   the periodicity of the thermal waves; and

               analyzing the second constituents in the
sample based on the output signal.

48.   A method as recited in claim 47 wherein the
modulation frequency of the pump beam is selected so
30   that the thermal diffusion length of the thermal
waves will be equal to approximately half the average
distance between the first constituents.

49.   A method as recited in claim 47 wherein the
modulation frequency of the pump beam is selected so

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that the thermal diffusion length of the thermal
waves will be equal to approximately (2/π) times the
average distance between the first and second
constituents.

5   50.   A method as recited in claim 47 wherein the
modulated power of the probe beam is monitored after
it has interacted with the sample.

         51.   A method as recited in claim 47 wherein the
modulated reflected power of the probe beam is
10   monitored.

         52.   A method as recited in claim 47 wherein the
modulated transmitted power of the probe beam is
monitored.

         53.   A method as recited in claim 47 wherein the
15   modulated scattering of the probe beam is monitored.

         54.   A method as recited in claim 47 wherein the
modulated changes in the polarization state of the
probe beam are monitored.

         55.   A method as recited in claim 47 wherein the
20   sample is blood and the first constituent is
hemoglobin and the second constituent is glucose and
wherein said probe beam is linearly polarized prior
to interacting with the glucose and wherein the
modulated polarization rotation of the beam is
25   monitored.

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56.   A method as recited in claim 47 wherein the
sample is blood and the first constituent is
hemoglobin and the second constituent is glucose and
wherein said probe beam is alternately left and
5   right-hand circularly polarized prior to interacting
with the blood stream and wherein the modulated ratio
of the transmitted left and right-hand circular
polarized light of the probe beam is monitored.

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57. A method for the non-invasive, in vivo
analysis of glucose carried in the blood stream of a
living mammal, said blood stream also carrying red
blood cells having hemoglobin therein, said method
5   comprising the steps of:
        generating a pump beam having a wavelength
    which is preferentially absorbed in the
    hemoglobin of red blood cells;
        intensity modulating said pump beam at a
10   predetermined frequency;
        directing the pump beam through the skin of
    the mammal and into the blood stream so that the
    energy of the pump beam is absorbed in the red
    blood cells in a manner to generate thermal
15   waves emanating therefrom, with the modulation
    frequency of the pump beam being selected so
    that the thermal waves extend beyond the
    hemoglobin and interact with the glucose in the
    blood stream;
20   generating a probe beam;
        directing the probe beam through the skin
    of the mammal and into the blood stream;
        monitoring the periodic changes in the
    probe beam caused by the thermal waves
25   interacting with the glucose in the blood stream
    and generating an output signal responsive
    thereto, and with the monitored periodic changes
    in the probe beam being approximately ninety
    degrees out of phase with the periodicity of the
30   thermal waves; and
        analyzing the concentration of glucose in
    the blood stream based on the output signal
    generated by said detector.

58. A method as recited in claim 57 wherein the
35   modulation frequency of the pump beam is selected so

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that the thermal diffusion length of the thermal
waves will be equal to approximately half the average
distance between red blood cells.

59. A method as recited in claim 57 wherein the
probe beam is linearly polarized prior to interacting
with the glucose and wherein the modulated
polarization rotation of the beam is monitored.

60. A method as recited in claim 59 wherein the
wavelength of the probe beam is selected to be in the
visible region.

61. A method as recited in claim 57 wherein
said probe beam is alternately left and right-hand
circularly polarized prior to interacting with the
blood stream and wherein the modulated ratio of the
transmitted left and right-hand circular polarized
light is monitored.

62. A method as recited in claim 61 wherein the
wavelength of the probe beam is selected to be in the
near infrared range.

63. A method as recited in claim 57 wherein
the wavelength of the pump beam is between 400 and
600nm.

64. A method as recited in claim 57 wherein the
modulation frequency of the pump beam is on the order
of 10 kHz.

65. A method as recited in claim 57 wherein the
modulated transmitted power of the probe beam is
monitored.

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66. A method as recited in claim 65 wherein the wavelength of the probe beam is selected to be in the visible range.

67. An apparatus for analyzing the properties
5   of a sample, said sample being non-homogenous and including at least first and second constituents, said apparatus comprising:

a first light source for generating an intensity modulated pump beam having a
10   wavelength which is preferentially absorbed in the first constituents;

means for directing the pump beam to interact with the sample to selectively induce a periodic heating in the first constituents in a
15   manner to generate thermal waves emanating therefrom, and wherein the modulation frequency of the pump beam is selected so that the thermal waves extend beyond the first constituents and interact with the second constituents;
20   a second light source for generating a probe beam;

means for directing the probe beam to interact with the sample;

a phase synchronous detector for monitoring
25   the periodic changes in the probe beam caused by the thermal waves interacting with the second constituents and generating an output signal responsive thereto, and with the monitored periodic changes being approximately ninety
30   degrees out of phase with the periodicity of the thermal waves; and

a processor for analyzing the second constituents in the sample based on the output signal from the detector.

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68. An apparatus as recited in claim 67 wherein the modulated transmitted power of the probe beam is monitored.

69. An apparatus as recited in claim 67 wherein the modulated changes in the polarization state of the beam are monitored.

70. An apparatus as recited in claim 67 wherein said probe beam is alternately left and right-hand circularly polarized prior to interacting with the sample and wherein said detector monitors the modulated ratio of the transmitted left and right-hand circular polarized light of the probe beam.

1 / 4
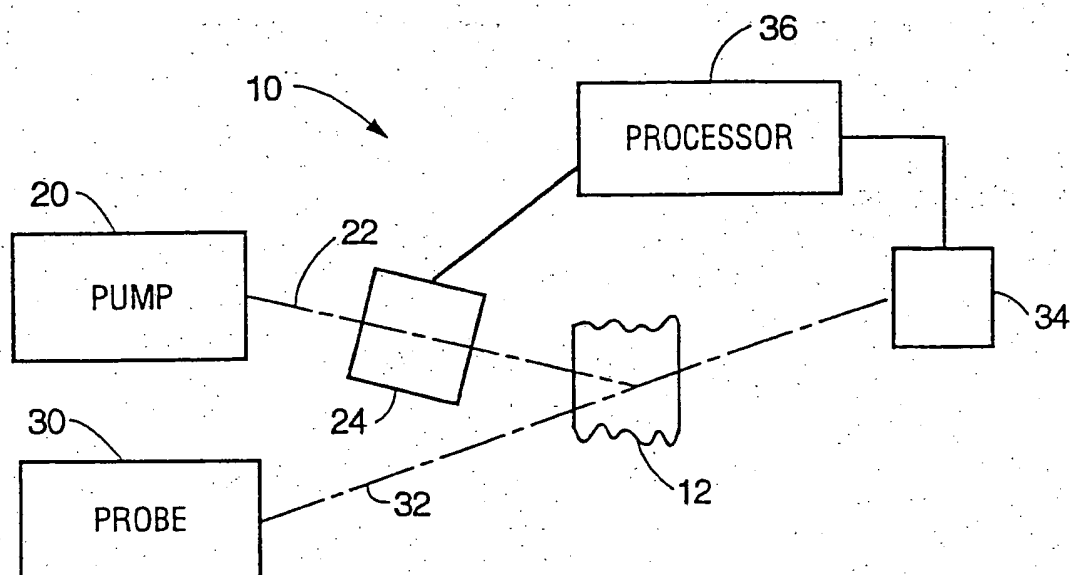
FIG. 1
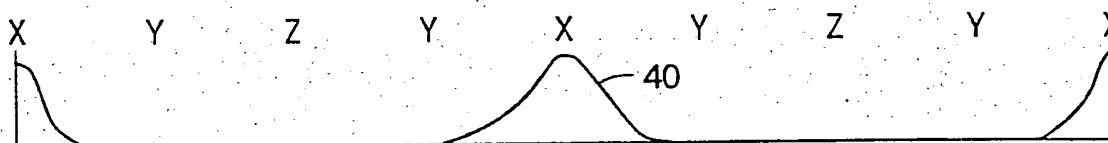
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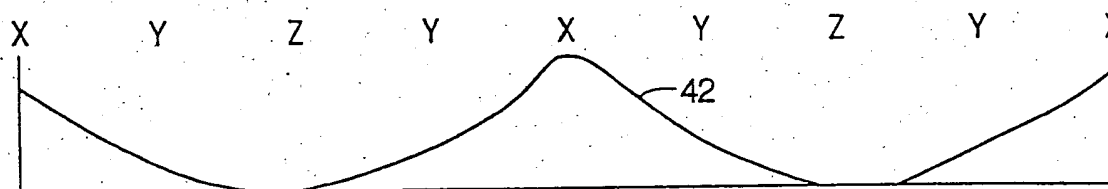
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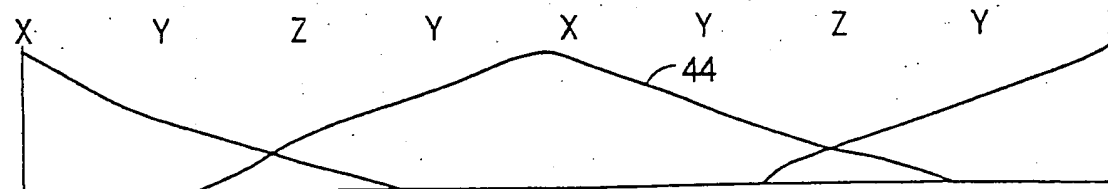
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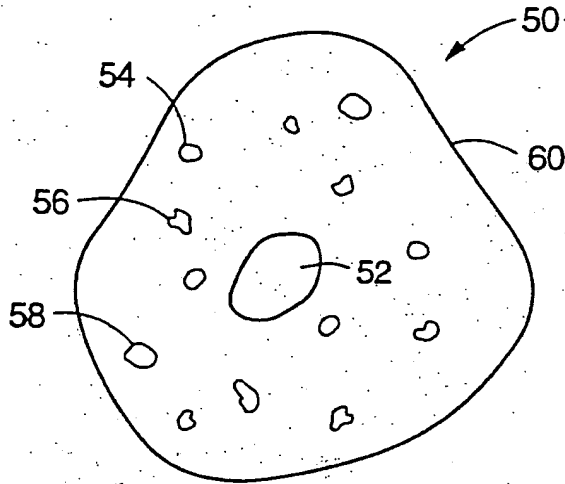
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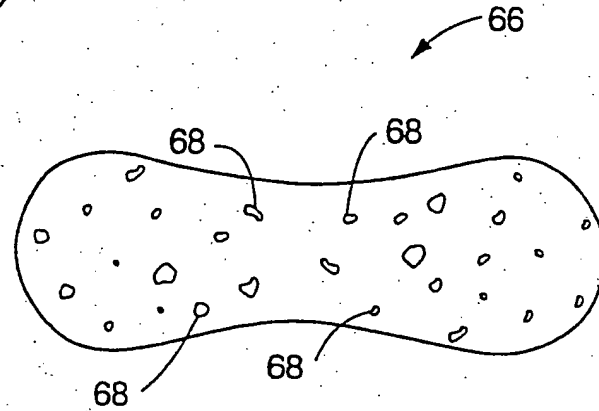
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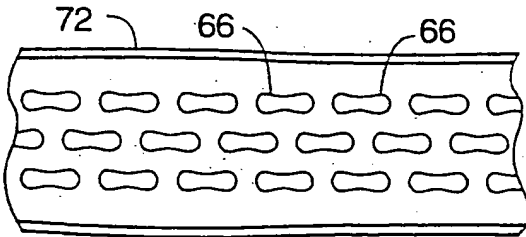
FIG. 5
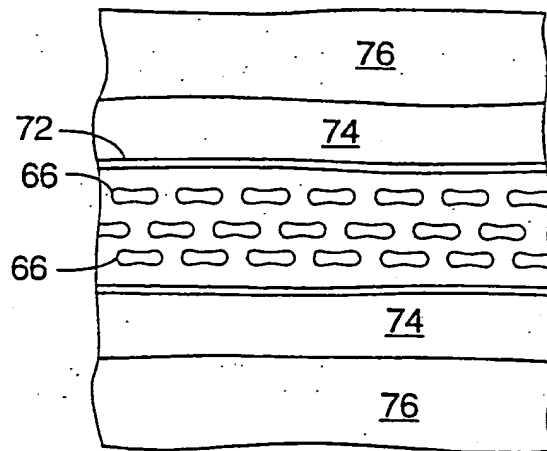
FIG. 7
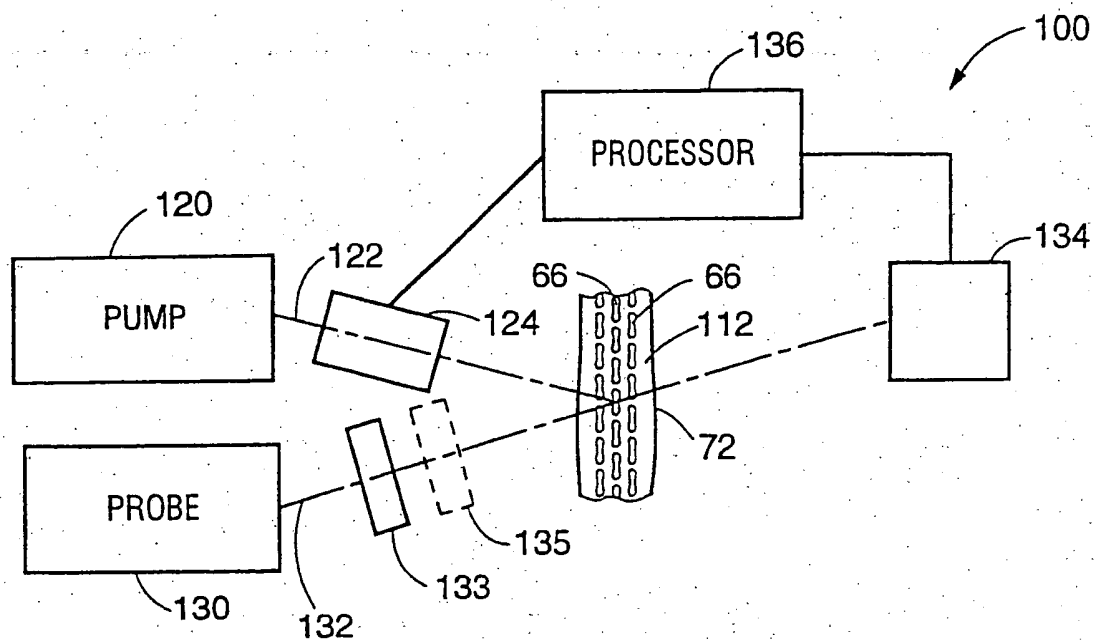
FIG. 6
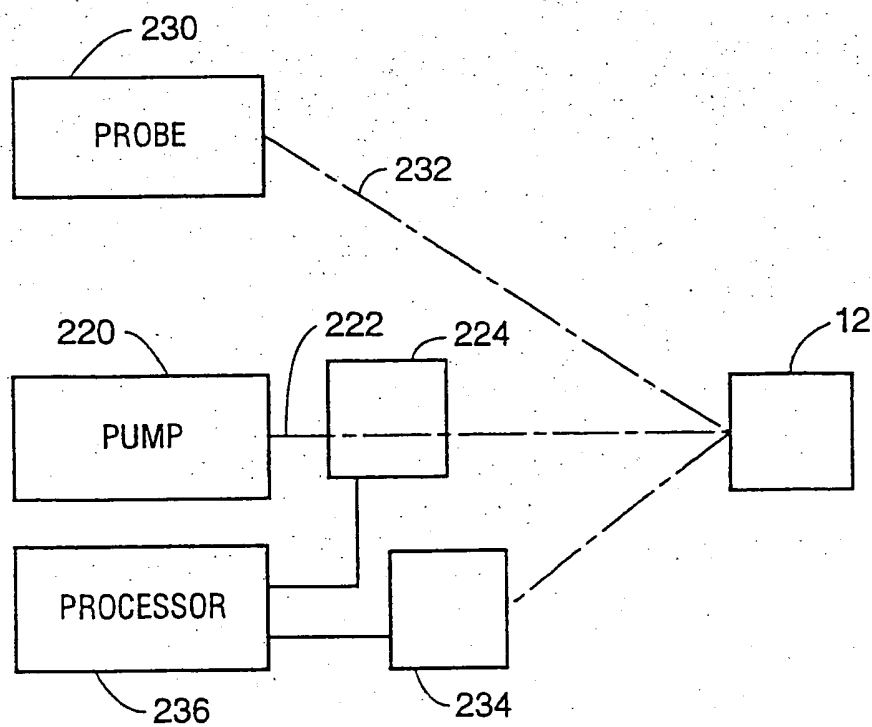
FIG. 8
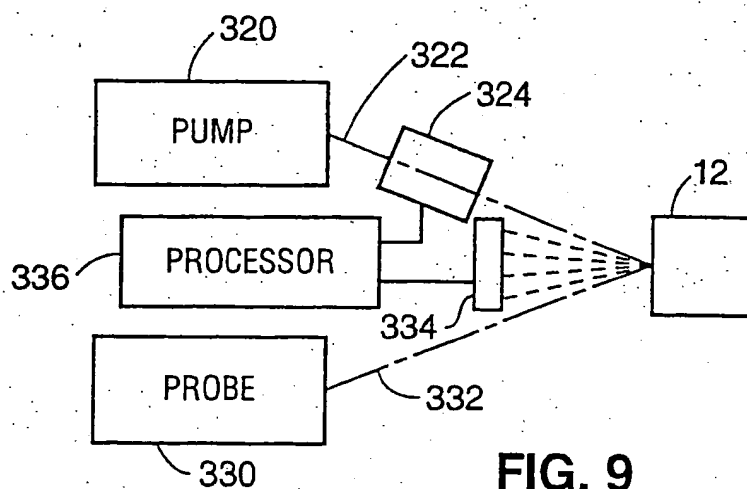
FIG. 9
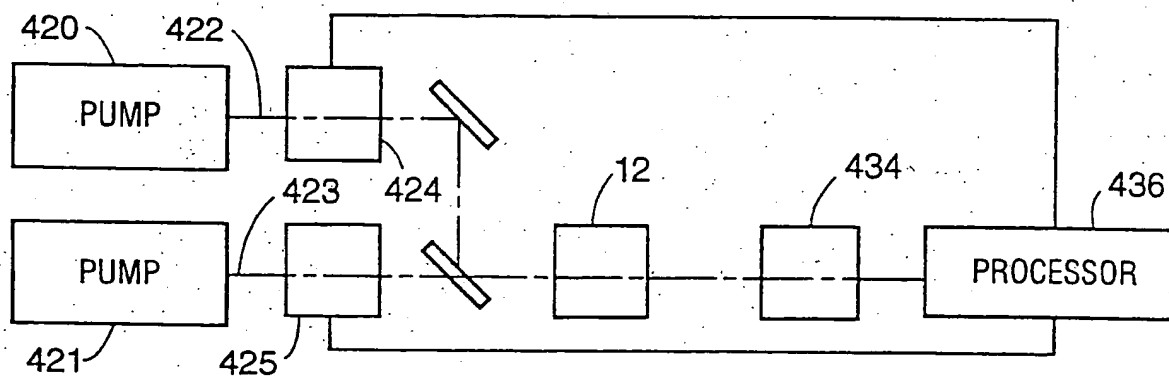
FIG. 10
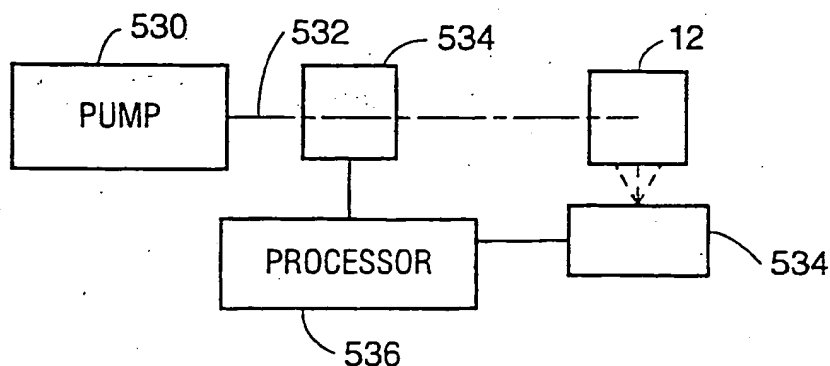
FIG. 11

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6   A61B5/00   G01N21/17   G01N25/00   G01N21/63

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6   A61B   G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,93 22649 (SIRRAYA INC) 11 November 1993 see page 6, line 6 - page 7, line 23 see page 10, line 8 - line 25 see page 11, line 25 - page 18, line 22 see page 25, line 4 - page 26, line 19 see figures 1-3,10,11	1,9
Y		10-21, 27-37, 39-47, 50-57, 59-70

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[X] Further documents are listed in the continuation of box C.   [X] Patent family members are listed in annex.

* Special categories of cited documents :

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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Date of the actual completion of the international search	Date of mailing of the international search report
16 October 1996	-4. 11. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Ferrigno, A

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page 1 of 2

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A		20,37, 47,57,67
X	--- US,A,3 948 345 (ROSENCWAIG ALLAN) 6 April 1976 see the whole document	1
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A	--- WO,A,92 10131 (GEORGIA TECH RES INST) 25 June 1992 see abstract	1,20,37, 47,57,67
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